Specialty Conference

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Granulomatous Giant Cell Angiitis of the Central Nervous System

JACK C. SIPE, MD:* An 81-year-old man was admitted to hospital because of deteriorating mental function. He was in good health except for mild cardiac difficulties for which he took quinidine and digoxin. Three years before admission a squamous cell carcinoma of the right part of the palate and tonsillar fossa was diagnosed and he was treated with 7,000 rads of local irriadiation followed by radical neck surgical procedures. On pathologic examination of the retromandibular lymph nodes, no evidence of metastatic carcinoma was found. For two years preceding admission the patient was noted to be occasionally forgetful and at times mildly confused. Five weeks before admission herpes zoster developed on the left side of the forehead and the patient was treated for two weeks with tapering doses of corticosteroids. Subsequently, severe lancinating facial pain occurred several times a day. Four weeks before admission, the patient noted a "top-heavy" sensation and required a cane for walking. He began falling without loss of consciousness or seizure activity and was admitted to hospital after suddenly falling out of a chair forward and to the right.

Findings on neurological examination included a relatively normal mental state, nystagmus on horizontal and vertical gaze, a mild pronation drift of the right arm and striking ataxia of the right arm and leg. The patient was unable to stand without assistance and consistently fell to the right. The deep tendon reflexes were normal in the arms, increased at the right knee compared with the left and absent at the ankles. The right plantar response was extensor, the left flexor. The sensory examination disclosed no consistent abnormalities. A diagnosis of brainstem lacunar infarction was made. Carbamazepine (Tegretol®) was given for postherpetic neuralgia with moderate success. A brain scan was normal.

Within two days of admission there was loss of the right arm drift and less right-sided ataxia. Truncal ataxia persisted, however, with continued falling to the right. A decline in mental facility was noted while the patient was in hospital; by the 17th hospital day the patient was oriented only to person and place and could follow only one part commands. On lumbar puncture slightly xanthochromic spinal fluid was found with an opening pressure of 150 mm of cerebrospinal fluid (CSF). There were 42 cells, predominantly lymphocytes, a protein value of 90 mg per 100 ml, and a glucose level of 55 mg per 100 ml. A Venereal Disease Research Laboratories (VDRL) study of CSF was nonreactive. Continued deterioration of mental state was evident and the patient was noted to intermittently confabulate. He rested in bed with his eyes closed and responded only to name.

On transfer of the patient to this hospital a physical examination showed normal vital signs and there was evidence that radical neck surgical procedures had been done several years before on the right. Patchy cutaneous pigmentation was noted in the left ophthalmic division of the trigeminal nerve. There was a nonradiating

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ABBREVIATIONS USED IN TEXT

ADH = antidiuretic hormone
CSF = cerebrospinal fluid
EEG = electroencephalogram
FTA = fluorescent treponemal antibody (test)
PML = progressive multifocal leukoencephalopathy
T_4 = thyroxine
TSH = thyroid stimulating hormone
VDRL = Venereal Disease Research Laboratories (test)

grade 2/6 systolic murmur at the left sternal border and the peripheral pulses were normal without detectable bruits. A prominent organic mental syndrome was present. This was characterized by orientation to person only, poor immediate and recent memory, and markedly decreased spontaneous speech. No aphasia was evident and he was able to follow only simple commands.

Neurological examination disclosed diffuse wasting and lead-pipe rigidity in the extremities. Symmetrical hyperreflexia was evident and the right plantar response was extensor, the left flexor. The patient was unable to walk or maintain his balance while seated. Positive glabellar, suck, snout and grasp reflexes were elicited bilaterally. The laboratory examination included a complete blood count with a leukocyte count of 9,100 cells per cu mm (92 segmental, 2 band forms, 1 lymphocyte and 5 monocytes). Studies of blood electrolytes on admission showed a sodium level of 122 mg per 100 ml, with a low serum osmolarity in the face of a high urine osmolarity. Blood urea nitrogen, calcium and glucose values were within normal limits. An x-ray study of the skull essentially showed no abnormalities except for an asymmetrical calcification in the left lateral ventricular area presumed to be a unilateral choroid plexus calcification. On repeat lumbar puncture there was clear, colorless fluid with a normal opening pressure; there was a protein level of 98 mg per 100 ml, a glucose value of 63 mg per 100 ml (simultaneous blood glucose value was 121 mg per 100 ml) and a negative VDRL test and a fluorescent treponemal antibody (FTA) study. There were 22 leukocytes, 100 percent lymphocytes and a cytologic examination for malignant cells was negative. Gram stain, routine cultures, fungus cultures and acid fast cultures were negative. CSF herpes simplex titer was 1:4; varicella-zoster 1:4. An electroencephalogram (EEG) done on the third hospital day showed a delta grade II, diffuse dysrhythmia. Findings on a repeat EEG one week later were essentially unchanged. The patient lay rigidly in bed with the eyes closed and pronounced flexion dystonia of the hips developed.

Results of repeat lumbar punctures showed a lymphocytic pleocytosis, elevated protein levels in the range of 100 mg per 100 ml and glucose values ranging slightly above 50 percent of the simultaneous blood glucose value. Cytologies, cultures and smears of the CSF were consistently negative. The patient's condition continued to deteriorate and he became unable to recognize his wife or sister. Skin tests for tuberculosis, candida and coccidioidomycosis were negative. An EMI® scan three weeks after admission showed mild cerebral atrophy. The thyroid stimulating hormone (TSH) level was 4.2 (normal) and the thyroxine (T_4) level was 1.4 μg per 100 ml. Therapy with sodium levothyroxine (Synthroid®), 25 μg per day, was started with no evident improvement in the clinical state. Despite fluid restriction, the syndrome of inappropriate antidiuretic hormone (ADH) secretion could not be corrected. CSF serologies were negative for cryptococcosis, aspergillosis, blastomycosis, candidiasis and coccidioidomycosis, and positive for histoplasmosis at 1:16. Convalescent CSF viral titers showed herpes simplex 1:4; varicella-zoster 1:64. A seven-day course of prednisone, 40 mg per day, was given but no neurologic improvement occurred. The patient died on the 52nd hospital day presumably of aspiration pneumonia.

Differential Diagnosis

JAY H. ROSENBERG, MD:* The patient is an 81-year-old man in whom nasopharyngeal carcinoma previously had been irradiated and in whom herpes zoster ophthalmicus developed. These events were followed by a progressive diffuse cerebral disorder. The striking positive laboratory findings in this case are three:

(1) The CSF herpes zoster titer rose from 1:4 on admission to 1:64 in the convalescent period.

(2) The patient was noted to have a low serum sodium level with a low serum osmolarity in the face of a high urine osmolarity. Inappropriate antidiuretic hormone secretion is the most likely condition to account for this combination of findings. Treatment could not fully correct

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the osmolarity and an x-ray study of the chest did not show the presence of a neoplasm. Findings on thyroid function tests were also found to be low with an initial T_4 value of 1.4 μg per 100 ml and a normal TSH level of 4.2.

(3) There was a persistent spinal fluid lymphocytic pleocytosis which is indicative of an inflammatory process involving the central nervous system.

A seven-day course of prednisone, 40 mg per day, was given in the terminal portion of the illness but there was no improvement and the patient died.

With a rise in the spinal fluid herpes zoster titer, could this entire process be explained as herpes zoster encephalitis? Generally, this uncommon disorder presents with a syndrome characterized by headache, ataxia, convulsions and coma.[1,2] In the acute stage there is usually a pronounced lymphocytic pleocytosis in the spinal fluid and cell counts of 60 to 450 are not unusual. Fever is frequently present; the spinal fluid protein level may be variable and viral cultures are commonly negative. In this patient, fever and convulsions were conspicuously absent. Certainly the diffuse encephalopathy could have been caused by herpes zoster meningoencephalitis. However, I would like to postulate that herpes zoster meningoencephalitis would not explain all the features of the patient's condition. There were, in addition to focal and diffuse neurological findings, inappropriate ADH secretion and involvement of the hypothalamic-pituitary axis.

The syndrome of inappropriate ADH secretion may be seen in the presence of encephalitis. In 1968, White and associates[3] reviewed their experience with St. Louis encephalitis in 52 patients. In this group, 18 of the 52 patients had an inappropriate ADH syndrome during their acute illness. It was concluded that the inappropriate ADH syndrome was an indication of some abnormality directly involving the brain parenchyma. Inappropriate ADH syndrome may be a nonspecific reaction to a wide variety of central nervous system diseases. Certain tumors may secrete ADH—the most common being oat cell carcinoma of the lung. However, in this patient findings on an x-ray study of the chest were negative, which would speak against the presence of a lung neoplasm. Although inappropriate ADH syndrome may be a nonspecific response, the presence of secondary hypothyroidism as a complication of viral encephalitis is exceedingly unusual. In their review of St. Louis encephalitis, White and associates[3] found that function of the pituitary-hypothalamic axis was undisturbed. The only change in the pituitary function is related to a general nonspecific stress reaction to the infection. Therefore, one could raise the possibility of an intraparenchymal process to account for the secondary hypothyroidism. If herpes zoster meningoencephalitis cannot account for all aspects of the condition, what are some alternative diagnostic possibilities?

With the past history of nasopharyngeal carcinoma, one must be concerned about the possibility of recurrent tumor. This commonly presents in the form of a locally invasive tumor with contiguous spread from the nasopharynx into the clivus or one of the sinuses to invade the brain. Generally, the presenting symptom is a progressive cranial neuropathy. In this patient there were no cranial nerve signs and, furthermore, no bony erosion was shown on x-ray films of the skull. Tomograms of the skull base would be helpful in excluding this diagnostic possibility. We are told that the EMI scan findings were normal but the EMI scan is less accurate in showing lesions at the base of the brain than supratentorial lesions.

One might raise the possibility of a carcinomatous meningitis but this is unlikely in view of the negative spinal fluid cytologies. Next, one must raise the possibility of some other type of infection with progressive diffuse involvement of the brain. The possibility of a brain abscess could be briefly considered, especially in the light of the persistent pleocytosis. However, against this are the normal brain scan findings, normal EMI scan results and the fact that the process was too diffuse. Could there have been multiple embolic infarctions from subacute bacterial endocarditis? This is a possibility in light of the fact that a heart murmur was noted at the time of this patient's admission but the time course was too long and fever was definitely lacking.

Could a tuberculous or fungal meningitis have been present? These are distinct possibilities but both skin tests and CSF cultures on several examinations were consistently negative for acid fast bacilli making tuberculous meningitis less likely. A thorough search was made for fungal meningitis; however, the CSF cultures were repeatedly negative and CSF serologies for cryptococcosis, aspergillosis, blastomycosis, candidiasis and coccidioidomycosis were negative. Further

evidence against the latter diagnoses was the presence of a normal CFS glucose value, which is usually but not invariably decreased in these chronic infections.

What other possibilities might be considered? Progressive multifocal leukoencephalopathy (PML) is another diagnostic consideration. The patient does have the background of preexisting carcinoma. In PML the involvement is commonly diffuse and asymmetric but usually involves the cerebral hemispheres and not the brain stem. This patient had both brain stem and hemispheric involvement. Absent was any visual impairment which is usually an early symptom in the course of PML. Other common findings include focal neurological deficits and an organic mental syndrome as was seen in this patient. However, against the diagnosis of PML is the fact that the pleocytosis is extremely unusual in this disease. The EMI scan in PML has been reported to show low density, asymmetrical lesions in the subcortical white matter that lack contrast enhancement.

If we have ruled out infection, recurrent tumor and PML, what other diffuse processes can one postulate that might be associated with herpes zoster in this patient? An intracranial arteritis or vasculitis certainly could explain this patient's deteriorating course. The association of a persistent spinal fluid pleocytosis and encephalopathic features raises this possibility. In the classification of vasculitis one must consider infection which has already been discussed. Other vasculitides include collagen-vascular disorders of which systemic lupus erythematosus is the most common, and necrotizing angiitis. Within the latter category are periarteritis nodosa, temporal arteritis and granulomatous giant cell arteritis of the brain. Other miscellaneous arteritides would include radiation vasculitis. Systemic lupus erythematosus presents with primary widespread involvement of the organs and is later followed by central nervous system complications. Personality change, confusion, organic mental syndrome and convulsions may be encountered in central nervous system lupus erythematosus. A cranial neuropathy may be seen but a peripheral neuropathy is more common. CSF pleocytosis may occur in systemic lupus erythematosus but one would expect systemic involvement including evidence of bone marrow and renal disease. Commonly periarteritis nodosa presents with headache, fever, skin rash, arthralgias, nasal symptons, coughing, wheezing, chills and night sweats. A skin rash and subcutaneous nodules are often present. Peripheral neuropathy is the most common neurological complication of periarteritis. In addition to the neuropathy, there may be central nervous system involvement in such cases but usually there are systemic findings of hematological and renal involvement. Aneurysmal dilatations or segmental occlusions of cerebral blood vessels may be seen in many of the vasculitides. We have no knowledge of the presence of aneurysmal dilatations due to the lack of information about this patient's blood vessels. In this patient a cerebral angiogram might have been a fruitful diagnostic procedure in that it might have shown either small vessel occlusion or aneurysmal dilatations of blood vessels.

The possibility of radiation-induced vasculitis affecting the major vessels at the base of the brain must be raised. The ports of radiation therapy in treating tumors of the nasopharynx may not be precise and scatter of irradition is possible. In one report, a fatal foam cell arteritis developed in a patient with Hodgkin disease following nasopharyngeal irradiation.[4] In that patient there was pronounced involvement of the hypothalamus and circle of Willis with the arteritis. The late delayed effects of radiation commonly occur between one and five years after treatment. Radiation arteritis is therefore a distinct possibility in the patient discussed today who previously received 7,000 rads of irradiation to the head region.

In the literature there has also been an association of herpes zoster with granulomatous giant cell arteritis of the nervous system.[5-7] Granulomatous arteritis is a necrotizing angiitis with the typical pathological signs in the blood vessels characterized by a granulomatous inflammation and giant cells. This condition commonly is characterized by headache, mental change, focal neurological abnormalities and spinal fluid pleocytosis.[8,9] Although this condition almost exclusively involves the intracranial vessels, the pathology is quite similar to temporal arteritis.

In summary, the progressive neurological disorder in this patient was most likely the result of an intracranial arteritis associated with herpes zoster, perhaps due to granulomatous angiitis or irradiation.

Pathological Discussion

DR. SIPE: The findings at general postmortem examination included bilateral bronchopneumonia due to aspiration, fibrosis of the thy-

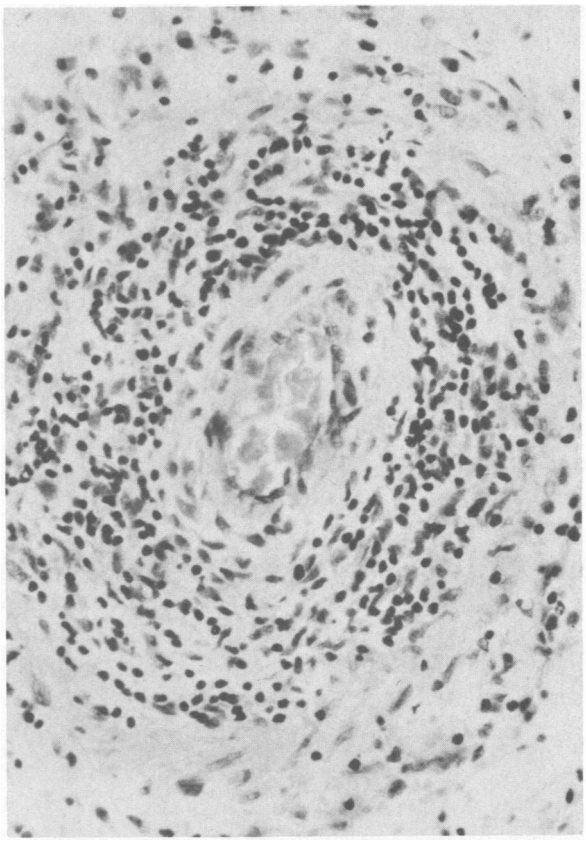

Figure 1.—This small vessel in the basal meninges illustrates the widespread findings of vasculitis. The angiitis is characterized by infiltration of the vessel wall with numerous lymphocytes, thickening of the tunica media and narrowing of the vascular lumen. (H & E×300)

roid gland and bilateral renal cysts. There was no evidence of recurrent or metastatic squamous cell carcinoma of the right tonsillar region. Microscopic examination of the organs, skin and skeletal muscle showed no inflammatory lesions save for the aspiration pneumonia.

The brain weighed 1,550 grams in the fixed state. The leptomeninges were diffusely thickened, fibrotic and opaque at the base of the brain, as well as over the convexities. The great vessels of the circle of Willis were enmeshed in the thickened meninges but there were no atherosclerotic plaques and the large vessels appeared otherwise grossly normal. Serial coronal sections through the cerebral hemispheres, cerebellum, brain stem and spinal cord disclosed multiple areas of softening and cavitation in the striatum and internal capsule bilaterally, the head of the left caudate nucleus, both thalami and especially in the dorsomedial and anterior nuclei bilaterally. Diffuse

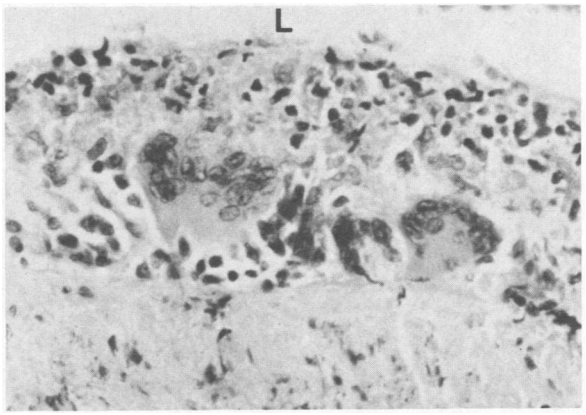

Figure 2.—Higher magnification view of a severely involved artery showing a cluster of multinucleated giant cells in the region of the vascular intima and internal elastic lamina. The area surrounding the giant cells is infiltrated by lymphocytes and histiocytes. L indicates vascular lumen. (H & E×350)

neocortical atrophy and mild enlargement of the ventricular system were present.

On microscopic examination of the basal leptomeninges and the meningeal vessels, there was the entire spectrum of necrotizing granulomatous angiitis, principally involving small and medium sized arteries (Figure 1) in a focal and patchy manner but also occasionally involving large arteries. In the involved vessels there was invasion of the adventitia, media and internal elastic lamina by lymphocytes, plasma cells and histiocytes together with accumulation of numerous giant cells in many involved arteries (Figure 2). Thrombosis and recannilization of many vessels was a prominent feature (Figure 3). Stains for bacteria, fungi and acid fast bacilli in involved vessels were negative. Elastic arterial stains showed complete disruption of the internal elastic lamina confirming the necrotizing character of the angiitis. Numerous old and recent ischemic infarctions were present in the neostriatum, thalamus, internal capsule and hippocampus on both sides. Active granulomatous arteritis together with thrombosed and recannilized arteries were evident in many infarcted zones especially in the putamen. There was no microscopic evidence of a systemic arteritis in any of the organs, skin or skeletal muscle. Therefore, results of the gross and microscopic neuropathological examinations, as well as the clinical and laboratory findings, support the diagnosis of granulomatous giant cell arteritis of the central nervous system.

This syndrome has been of considerable interest since the early reports of Wolfe and New-

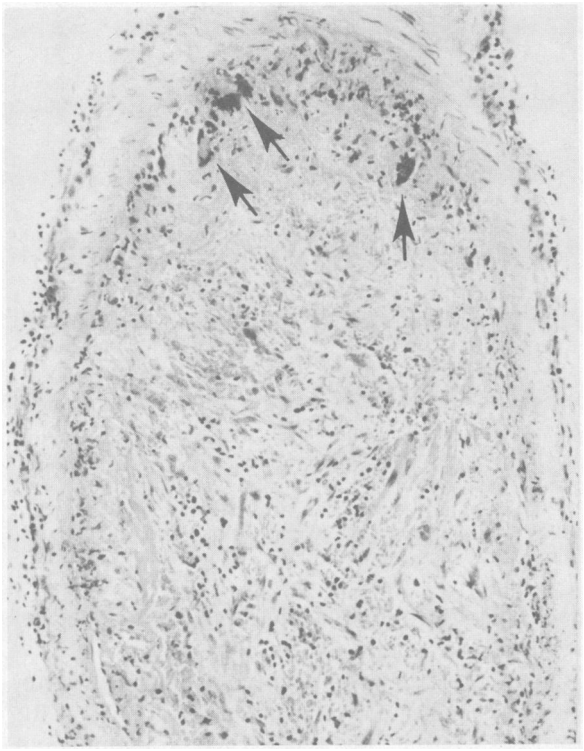

Figure 3.—A medium sized meningeal vessel illustrating thrombosis of the lumen together with an active vasculitis and multinucleated giant cell accumulation (arrows). (H & E×130)

man[10] and Cravioto and Feigen.[11] The distinctive pathological features are the striking predilection for the central nervous system without evidence of angiitis elsewhere. In most reported cases, a noninfectious granulomatous angiitis involves small and medium sized arteries. This distinguishes the disease from many other forms of vasculitis that may simultaneously involve both intracranial and extracranial vessels. A highly focal and random pattern in the central nervous system with predilection for the meningeal vessels, vessels of the cerebral cortex, basal ganglia and spinal cord has been reported.[6-12] Histologically, most reported cases are quite similar to the present case.

The cause and pathogenesis remain completely unknown despite several recent reports. Although the granulomatous inflammation suggests invasion by microorganisms, none have been identified.[13] The angiitis resembles histologically that seen in temporal arteritis and allergic granulomatosis.[13] The present disease can be distinguished because the angiitis is almost exclusively confined to the central nervous system. Several reported cases of granulomatous giant cell angiitis of the CNS have been associated with lymphoreticular malignancies and herpes zoster infection.[5-7] The association of herpes virus infection and giant cell granulomatous arteritis is of particular interest because of the well known ability of viruses to induce the formation of syncitia in tissue culture. This suggests a possible mechanism for multinucleated giant cell development. Electron microscopic studies seeking virus-like particles are limited to the study of Reyes and associates[14] who found intranuclear "virus-like" particles in glial cells from a formalin-fixed postmortem brain specimen. However, to be convincing the latter study's findings must await confirmation by other techniques such as immunofluorescent staining or viral isolation because of the well known difficulties encountered in the interpretation of "virus-like" particles in postmortem brain specimens.[15]

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